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TITLE: MOISTURE CURABLE BALLOON MATERIALS

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MOISTURE CURABLE BALLOON MATERIALS

FIELD OF THE INVENTION

The present invention relates to the preparation of thin films useful in

5   medical devices, and in particular in the manufacture of medical dilatation balloons,

formed from a durable polymeric composition crosslinked upon exposure to moisture

through --Si--O--Si-- linkages. More particularly, the balloons are formed from the

reaction product of at least one organofunctional hydrolyzable silane and at least one

polymer, the reaction product of which is crosslinked by exposure to moisture. The

10   crosslinked structure increases the toughness, abrasion resistance, durability and

dimension stability of the material during both manufacturing procedures and during use.

BACKGROUND OF THE INVENTION

Balloon catheters are used in procedures relating to the treatment of

15   stenoses or blockages in body vessels, an example of which is an arterial stenosis which

is commonly treated by angioplasty procedures which involve the insertion of balloon

catheters into the affected blood vessel of the patient.

The balloon may function to widen a vessel into which the catheter is

inserted, to force open a blocked vessel to open the blocked or collapsed blood vessel, or

20   to prop open the a collapsed vessel. The requirements for strength and size of the

balloons vary widely depending on the balloon's intended use and the vessel size into

which the catheter is inserted. Perhaps the most demanding applications for such

balloons are in balloon angioplasty in which catheters are inserted for long distances into

extremely small vessels and used to open stenoses of blood vessels by balloon inflation.

25   Balloon angioplasty requires extremely thin walled, high strength (i.e.

high tensile), relatively inelastic balloons of predictable inflation properties.

Thin walls are necessary because the balloon's wall and waist thicknesses

limit the minimum diameter of the distal end of the catheter and therefore determine the

limits on vessel size treatable by the method and the ease of passage of the catheter

30   through the vascular system. High strength is necessary because the balloon is used to

push open a stenosis and so the thin wall must not burst under the high internal pressures

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necessary to accomplish this task. The balloon must have some elasticity so that the inflated diameter can be controlled, so as to allow the surgeon to vary the balloon's diameter as required to treat individual lesions, but that elasticity must be relatively low so that the diameter is easily controllable. Small variations in pressure must not cause

5   wide variation in diameter.

To achieve the high strength, thin walled properties, catheter balloons are often made of biaxially oriented polyethylene terephthalate (PET) or a polyamide material such as nylon 12. These materials, however, tend to be less elastic, and have less resilience.

10   Balloon catheters may also be made of more elastic materials such as polyolefins or polyolefin copolymers, but typically, in order to achieve the high tensile strength, the balloon walls must be made thicker.

One difficulty experienced in the case of the high strength, thin walled materials, such as PET is that they can be punctured through abrasion or the like, even

15   though they have a high tensile strength. Pin holes and ruptures can occur when such catheter balloons are used in contact with rough surfaces. Also, tiny flaws in the mold of such balloons can create weak spots, since the balloons are so thin-walled.

It is, however, typically impractical to increase the wall thickness of these biaxially oriented, non-resilient materials because they become too stiff, with high

20   flexural moduli, with the result that such balloons do not collapse properly on deflation to facilitate easy withdrawal from the vascular system of a patient.

The balloons can be coated with a more abrasion resistant material, but coatings add a step during the manufacturing process, typically decrease flexibility, and also typically increase the wall thickness.

25   There remains a need for a balloon catheter which is thin walled, durable, abrasion and tear resistant thereby improving the resistance to pinhole formation, and is relatively flexible, yet inelastic to allow the balloons to expand outwardly to a predetermined diameter, and then cease further expansion at normal pressures, to avoid damage to the artery wall by overexpansion.

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SUMMARY OF THE INVENTION

The present invention relates to a medical device such as a balloon catheter comprising a dilatation balloon wherein said balloon comprises a moisture cured polymeric material which is crosslinked through --Si-O-Si-- linkages.

5   The present invention further relates to a catheter balloon comprising the reaction product of at least one polymer and at least one organofunctional hydrolyzable silane having an organofunctional group capable of readily reacting with the moieties on the polymer backbone. The silane is grafted onto the polymer backbone and the hydrolyzable groups of the silane are activated by moisture, crosslinking the structure

10   through --Si-O-Si-- linkages.

The present invention further relates to a medical device comprising a dilatation balloon formed from a crosslinked polymeric material, the crosslinked polymeric material comprises the reaction product of at least one polymer and at least one hydrolyzable silane having the following general structure:

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$$X-\underset{\underset{Z\ (3\text{-}m)}{|}}{Si}-Y_m$$
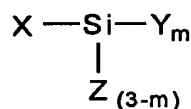
where X is a monovalent non-hydrolyzable organic moiety comprising at least one

20   functional group W which is reactive with said polymer with the proviso that an Si-C bond is present between Si and W, Y is a hydrolyzable group, Z is a monovalent hydrocarbon group, and m is an integer from 1 to 3. The hydrolyzable silane groups, Y of the silane are then activated with moisture to form a durable, tough, high strength, excellent abrasion resistant polymeric material crosslinked through --Si--O--Si--

25   linkages. The balloon structure also has dimension stability during both manufacturing procedures and in use. The high strength crosslinked material allows the balloons to be manufactured having of a relatively thin walled structure.

The present invention further relates to a method of forming a catheter balloon comprising the steps of providing at least one polymeric material at or above its

30   melt temperature, providing at least one organofunctional hydrolyzable silane compound, extruding the polymeric material and the organofunctional hydrolyzable silane

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compound into a tubular preform at a temperature wherein the polymeric material and the hydrolyzable silane react, forming the tubular preform into a balloon preform, blowing the balloon preform into a balloon, and exposing the balloon or balloon preform to water. The hydrolyzable groups on the silane are activated by moisture forming a

5   durable polymeric material crosslinked through --Si--O--Si-- linkages..

BRIEF DESCRIPTION OF THE DRAWINGS

Fig. 1 is a perspective view of a dilatation catheter having attached at its distal end, a catheter balloon of the present invention depicted in its inflated state.
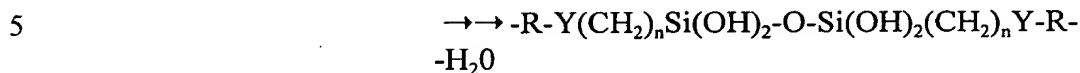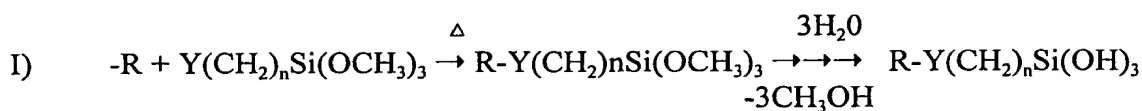
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DETAILED DESCRIPTIONS OF THE PREFERRED EMBODIMENTS

The present invention relates to medical balloons that are made of a durable polymeric material crosslinked through --Si-O-Si-- linkages.

The method of preparing the medical balloons of the present invention

15   involves the grafting of hydrolyzable silanes onto a polymer backbone and then moisture curing the resultant polymeric structure. The hydrolyzable groups of the silane are activated upon exposure to moisture forming durable --Si--O--Si-- linkages.

The general reaction scheme representative of the grafting/moisture curing reaction of the present invention generally involves a two-step reaction process in which

20   the first step is the reaction between the hydrolyzable silane compound and the polymer at melt in the absence of moisture, and the second step is the crosslinking reaction in which the hydrolyzable groups of the silane are activated with moisture forming the durable --Si--O--Si-- linkages.

This two step process can be represented by the following general reaction

25   scheme. The first step of the diagram illustrates the reaction between the polymer and the hydrolyzable silane compound. The second and third reactions illustrate hydrolysis and condensation of the polymer to form the --Si--O--Si-- linkages. The latter two reactions occur basically simultaneously and are considered to be the second step.

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$$\text{I)} \quad -R + Y(CH_2)_nSi(OCH_3)_3 \xrightarrow{\Delta} R-Y(CH_2)nSi(OCH_3)_3 \xrightarrow[-3CH_3OH]{3H_2O} R-Y(CH_2)_nSi(OH)_3$$

$$\xrightarrow[-H_2O]{} -R-Y(CH_2)_nSi(OH)_2-O-Si(OH)_2(CH_2)_nY-R-$$

The silanes useful herein include those having hydrolyzable groups, each of which is bonded to the silicon atom and that will effectively graft and crosslink to a polymer backbone. Hydrolyzable groups include C_1 to C_{12} alkoxy groups, in particular the lower C_1 to C_4 alkoxy groups such as methoxy or ethoxy, C_2 to C_4 acryloxy, up to about C_6 (poly)alkoxyalkoxy, phenoxy, oxime, amine, halogen groups including chlorine, fluorine and bromine, and so forth. In particular emodiments of the present invention, hydrolyzable groups including the alkoxy, alkoxyalkoxy and the acryloxy groups are used. The hydrolyzable groups, the alkoxy groups for instance, will be activated by moisture to form durable structures crosslinked through --Si--O--Si-- linkages.

The organofunctional hydrolyzable silanes useful herein may be broadly represented by the following general structure:

$$\text{II)} \qquad X-\underset{\underset{Z_{(3-m)}}{|}}{Si}-Y_m$$

where X is a monovalent non-hydrolyzable organic moiety comprising at least one functional group W which is reactive with the polymeric material to which the silane is to be grafted with the proviso that at least one Si-C bond is present between Si and W, Y is a hydrolyzable group, Z is a monovalent hydrocarbon group, and m is an integer from 1 to 3. The hydrolyzable silane is useful from about 0.05 wt-% to about 20 wt-% of the polymer/silane composition.

W may be, but is not limited to, (meth)acrylamido, (meth)acryloxy, carboxyl, epoxy, amino, ureido, isocyanato, thiocyanato, mercapto, haloalkyl, styryl,

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vinyl, allyl, sulfonyl azide, acid anhydride, or carboxylic acid esters of aromatic alcohols, the alcohols of which have 2 to 15 carbon atoms, and mixtures thereof.

In particular embodiments X is epoxycylohexyl, glycidoxypropyl, isocyanatopropyl, vinyl or allyl. Other examples of X include, but are not limited to,

5 3-acryloxypropyl, 3-methacryloxypropyl, 3-glycidoxypropyl, 2-(3,4-epoxycyclohexyl)ethyl, 3-aminopropyl, N-(2-aminoethyl)-3-aminopropyl, (aminoethylaminomethyl)phenethyl, 3-(1-aminopropoxy)-3,3-dimethyl-1-propenyl, N-phenylaminopropyl, diethylenetriaminopropyl, and 3-ureidopropyl. Organofunctional moieties containing amino functional groups or isocyanato functional groups are

10 particularly versatile in having reactivity or compatibility with a wide range of different polymer types.

In particular embodiments, Y is C_1 to C_4 alkoxy, and m is 2 or 3.

Some examples of specific unsaturated silanes represented by formula II) above that are useful herein include, but are not limited to, those that comprise an

15 ethylenically unsaturated hydrocarbyl group, such as a vinyl, allyl, isopropenyl, butenyl, cyclohexenyl or γ-(meth)acryloxyalkyl group, and a hydrolyzable group, such as, for example, a hydrocarbyloxy, hydrocarbonyloxy, or hydrocarbylamino group. Examples of hydrolyzable groups include methoxy, ethoxy, formyloxy, acetoxy, proprionyloxy, and alkyl or arylamino groups.

20 Preferred silanes of this category are the unsaturated alkoxy silanes which can be grafted onto the polymer.

Some of these unsaturated silanes and their method of preparation are more fully described in US 5312861 and US 5266627, both of which are incorporated by reference herein in their entirety. Specific examples of these silanes for use herein are

25 vinyl trimethoxy silane, vinyl triethoxy silane, γ-(meth)acryloxy propyl trimethoxy silane, allyltrimethoxysilane, and so forth.

A particular class of hydrolyzable silanes useful herein include those represented by the following general formula:

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III) $CH_2 = C \overset{R'}{\underset{|}{{\Big(}}} \overset{O}{\underset{\|}{C}} - O (C_n H_{2n})_y {\Big)}_x SiR_3$

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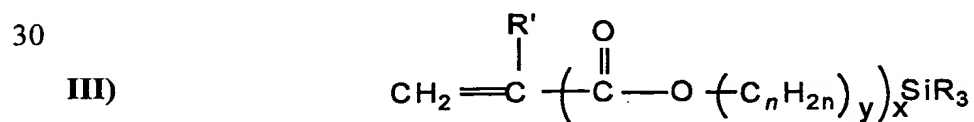
where R' is a hydrogen atom or lower C_1 to C_4 alkyl, particularly methyl; x and y are 0 or 1 with the proviso that when x is 1, y is 1; n is an integer from 1 to 12 inclusive, preferably 1 to 4, and each R independently is a hydrolyzable organic group such as an

5 alkoxy group having from 1 to 12 carbon atoms (e.g. methoxy, ethoxy, butoxy), aryloxy group (e.g. phenoxy), araloxy group (e.g. benzyloxy), aliphatic acyloxy group having from 1 to 12 carbon atoms (e.g. formyloxy, acetyloxy, propanoyloxy), amino or substituted amino groups (alkylamino, arylamino), or a lower alkyl group having 1 to 6 carbon atoms inclusive, with the proviso that not more than one of the three R groups is

10 an alkyl.

Other silanes useful herein include but are not limited to, 3-acryloxypropyltrimethoxysilane, 3-methacryloxypropyltimethoxysilane, 3-methacryloxypropyltris(methoxyethoxy)silane, 3-glycidoxypropyltrimethoxysilane, (3-glycidoxypropyl)methyldiethoxysilane, 3-aminopropyltriethoxysilane,

15 2-(3,4-epoxycyclohexyl)ethyltrimethoxysilane, (3-aminopropyl)methyldiethoxysilane, N-(2-aminoethyl)-3-aminopropyltrimethoxysilane, N-(2-aminoethyl)-3-aminopropylmethyldimethoxysilane, (aminoethylaminomethyl)phenethyltrimethoxysilane, 3-(1-aminopropoxy)-3,3-dimethyl-1-propenyltrimethoxysilane,

20 N-phenylaminopropyltrimethoxysilane, (3-trimethoxysilylpropyl)diethylenetriamine, ureidopropyltriethoxysilane, 3-isocyanatopropyltriethoxysilane, 3-thiocyanatopropyltriethoxysilane, 3-mercaptopropyltriethoxysilane, 3-(N-styrylmethyl-2-aminoethylamino)propyltrimethoxysilane hydrochloride, phenyltriethoxysilane, phenethyltrimethoxysilane,

25 (p-chloromethyl)phenyltrimethoxysilane, (chloromethyl)phenylethyltrimethoxysilane, and so forth.

Suitable polymers include, but are not limited to, polyolefins such as polyethylene and polypropylene, and substantially linear ethylene and propylene α-olefins; acrylic polymers; copolymers of olefins and acrylic acid ester copolymers

30 thermoplastic or elastomeric polyurethanes; thermoplastic or elastomeric polyesters; polyamides; polysulfones; polyvinyls; and so forth.

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The incorporation of silanes into polyamides, as well as other polymers including polyolefins, is discussed in US 4637640 and in US 5055249 both of which are incorporated by reference herein in their entirety.

Some specific embodiments of the present invention are represented by

5   the following reaction mechanisms. In some specific embodiments, an amino functional polymer, is reacted with an isocyanate functional hydrolyzable silane. Poly(meth)acrylate polymers having pendant hydroxy groups thereon can be also be reacted with isocyanato functional alkoxysilanes. These types of reactions have been found to have particular utility herein.
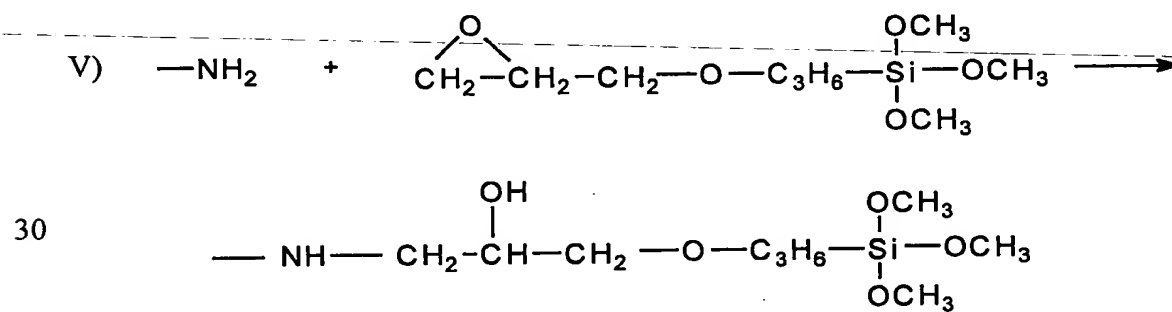
10   For instance, an example of a reaction between the isocyanate functional silane compound, isocyanatopropyltriethoxy silane, and an amine containing polymer may be represented by the following general reaction scheme:

IV)

15   $-NH_2$ + $O=C=N-CH_2CH_2CH_2-Si(OCH_3)(OCH_3)-OCH_3$ $\longrightarrow$

$-NH-C(=O)-N(H)-CH_2CH_2CH_2-Si(OCH_3)(OCH_3)-OCH_3$

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An example of a reaction in which a silane compound having epoxy functionality is reacted with a polymer having amine functionality may be represented by

25   the following general reaction scheme:

V) $-NH_2$ + $\underset{\displaystyle \overset{O}{\diagup\diagdown}}{CH_2-CH_2-CH_2}-O-C_3H_6-Si(OCH_3)(OCH_3)-OCH_3$ $\longrightarrow$

30   $-NH-CH_2-\underset{OH}{CH}-CH_2-O-C_3H_6-Si(OCH_3)(OCH_3)-OCH_3$
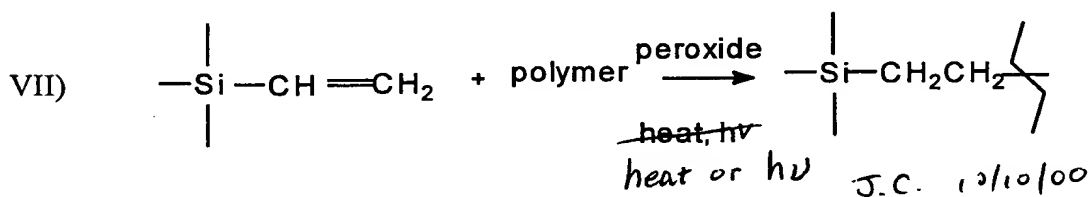
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Another example of a reaction between a different epoxy functional silane and a polymeric amine containing compound may be represented by the following general reaction scheme:

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VI)

$$\text{—NH}_2 \quad + \quad \text{(epoxycyclohexyl)}\text{—CH}_2\text{—CH}_2\text{—Si(OCH}_3)_3 \quad \longrightarrow$$

10

$$\text{(cyclohexyl with —NH and OH)}\text{—CH}_2\text{—CH}_2\text{—Si(OCH}_3)_3$$
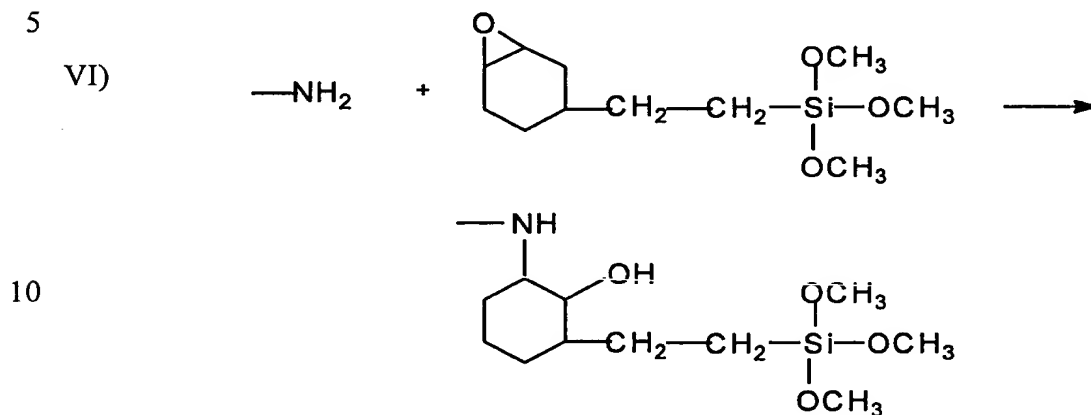
A specific method of grafting an unsaturated hydrolyzable silane onto the

15 backbone of a polymer is by a free radical mechanism in which a free radical initiator, such as an organic peroxide, is used.

The following reaction mechanism is representative of an unsaturated silane, i.e. in this case a vinyl containing silane, reacted onto a ~~polmer~~ polymer backbone by a free radical mechanism using a peroxide as the free radical initiator. _polymer J.C. 10/10/00_

20

VII)

$$\text{—Si—CH}=\text{CH}_2 \quad + \quad \text{polymer} \xrightarrow[\substack{~~heat, hv~~ \\ \text{heat or } h\nu}]{\text{peroxide}} \quad \text{—Si—CH}_2\text{CH}_2\text{—}$$

_J.C. 10/10/00_

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The second part of the reaction process is a moisture curing step in which the hydrolyzable alkoxy groups of the silane in the presence of moisture, react to form polymers which are crosslinked by the presence of --Si--O--Si-- linkages. These crosslinked polymers provide structures which are more durable, abrasion resistant, tear

30 resistant and dimensionally stable during sterilization than non-crosslinked polymeric materials.

The resultant crosslinked material finds particular utility in medical devices, especially in angioplasty catheter balloons where the durability and toughness are especially important.

In the preparation of the medical devices of the present invention, a

5   tubular preform is first prepared by mild blending and extruding the amine containing polymeric material and the functional silane compound together at a temperature of greater than the metling temperature of the polymer(s) in the absence of moisture. The tubular preform may be prepared using any extrusion techniques known in the art.

The tubular preform may then be fed into a balloon mold. The balloon is

10   then exposed to moisture in some form in order to produce the crosslinked balloon structure of the present invention. This exposure to moisture may occur by actually forming the balloon in a water bath at temperatures and pressures typically used for balloon formation, or it may occur after balloon formation, for instance by placing the already formed balloon in a water bath with or without pressure.

15   Balloons are typically formed using a blow molding technique. However, balloon formation may be carried out in any conventional manner with conventional extrusion and blowing techniques, but basically there are three major steps in the process which include extruding the tubular preform, blow molding the balloon and annealing the balloon. The preform may be axially stretched and/or biaxially oriented before it is

20   blown. General techniques for balloon formation are discussed in U.S. Patent No. 4,490,421 to Levy and in U.S. Patent no. 5,348,538 issued September 20, 1994 to Wang et al. Fig. 1 is a perspective view of dilatation catheter shown in its inflated state having attached at its distal end a catheter balloon shown generally at 10. Catheter balloon 14 is formed of the crosslinked polymeric material of the present invention and is conventional

25   in its structure having a body portion 12, cone portions 14 and waist portion 16. One of skill in the art will recognize that the moisture cured polymeric materials of the present invention may be utilized in any catheter balloon configuration capable of being formed from a polymeric material, and that numerous modifications can be made to these structures without departing from the spirit and scope of the present invention.

30   The exposure of the alkoxy groups of the silane to moisture results in the crosslinking reaction. After forming, the balloon may be kept in the hot water bath under

pressure and tension at conventional molding temperatures such as in the range of about 65° C to about 145° C for a predetermined time to ensure completion of the crosslinking process. Any remaining uncrosslinked functional groups, however, will undergo crosslinking over time.

5   The resultant process for manufacturing the improved balloons of the present invention is thus very simple without the introduction of extra steps into the process of preparing the tubular preform.

As compared to some prior art methods, there is no requirement for radiation or e-beams using the method of the present invention. One disadvantage

10   known to using e-beams is that it is difficult to get a full cure without any chain scission occuring. Further, the e-beam process is not economical.

The embodiments described herein are in no way intended to limit the present invention and one of skill in the art will recognize that modifications can be made without departing from the spirit and scope of the present invention.

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